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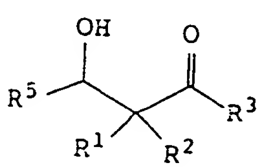
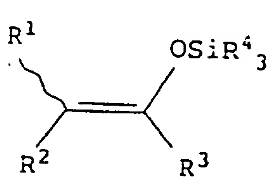
(54) Process for producing optically active beta-hydroxyketone.

(57) A process for producing an optically active β- hydroxyketone represented by formula (I) :



(I)

by catalytic asymmetrical aldol reaction comprises reacting a silyl-enol ether represented by formula (II) :



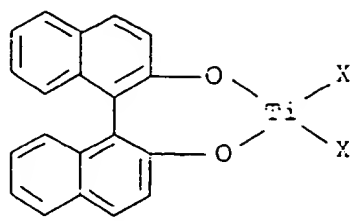
(II)

with a substituted aldehyd repres nted by formula (III) :

$$R^5CHO \qquad (III)$$

in the pres nce of a binaphthol-titanium complex repres nted by formula (IV) :

EP 0 614 871 A1



(IV)

R^1-R^5 are lower alkyl etc as defined in the specification.

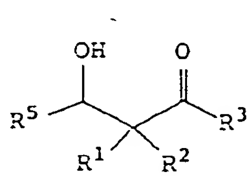
An optically active β-hydroxyketone is efficiently produced with diastereo-specificity and enantio-specif icity and is useful as an intermediate for preparing biologically active substances in the medical and pharmaceutical fields.

This invention relates to a process for producing an ptically activ β-hydroxyk ton of formula (I) shown below by an asymmetrical aldol reaction in the presence of a catalyst. The ptically active β-hydr xyketon is useful, for example, as an intermediate for biologically activ substances in th medical and pharmaceutical fields since it has a plurality of functional groups.

Known processes for preparing an optically active β-hydroxyketone (an optically active alcohol) through a catalytic asymmetrical aldol reaction include (1) reaction between an aldehyde and a silyl-enol ether in the presence of a binaphthol-oxotitanium complex (see T. Mukaiyama, et al., Chem. Letter., pp. 1015-1018 (1990)), (2) reaction between an aldehyde and a silyl-enol ether in the presence of a boron complex derived from tartaric acid (see K. Furuta, et al., Syn. Lett., pp. 439-440 (1991)), (3) reaction between an aldehyde and a silyl-enol ether in the presence of a boron complex derived from menthone (see E.R. Parmee, et al., Tetrahedron Lett., Vol. 33, pp. 1729-1732 (1992)), and (4) reaction between an aldehyde and nitromethane in the presence of a binaphthol lanthanoid complex (see H. Sakai et al., J. Am. Chem. Soc., Vol. 114, pp. 4418-4420 (1992)). However, these conventional processes were unsatisfactory in terms of catalytic activity and optical purity (diastereo-selectivity or enantio-selectivity). Besides, preparation of the above-mentioned complex catalysts involves complicated operation.

As a result of extensive investigations, the present inventors have found that an optically active β-hydroxyketone can be obtained efficiently with high diastereo-selectivity and high enantio-selectivity by using an optically active binaphthol-titanium complex.

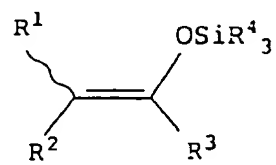
The present invention relates to a process for producing an optically active β-hydroxyketone represented by formula (I):



(I)

wherein R^1 and R^2, which may be the same or different, each represent a hydrogen atom or a lower alkyl group; R^3 represents a lower alkyl group, a lower alkyloxy group, a phenyl group, a phenyloxy group or a lower alkylthio group; and R^5 represents a lower alkyl group, a lower alkyloxymethyl group, a benzyloxymethyl group or a lower alkyloxycarbonyl group,

comprising reacting a silyl-enol ether represented by formula (II):



(II)

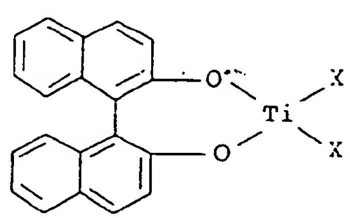
wherein R^1, R^2, and R^3 are as defined above; and three R^4s, which may be the same or different, each represent a lower alkyl group or a phenyl group,

with a substituted aldehyde represented by formula (III):

$$R^5CHO \qquad (III)$$

wherein R^5 is as defined above,

in the presence of a binaphthol-titanium complex represented by formula (IV):



(IV)

wher in X r pres nts a chl rine atom or a bromine atom.

In f rmula (I), (II), and (III), the termin logy "lower" means from 1 to 5 carbon atoms forming a straight r branched carbon chain.

The silyl group ($-SiR^4_3$) in f rmula (II) includes a trimethylsilyl group, a triethylsilyl group, a tri-n-propylsilyl group, a tri-n-butylsilyl group, a tri-n-pentylsilyl group, a t-butyldimethylsilyl group, a triisopropylsilyl group, a dimethylisopropylsilyl group, a phenyldimethylsilyl group, and a triphenylsilyl group.

To take an instance, specific examples of the silylenol ether of formula (II) wherein the silyl group is a trimethylsilyl group are methyl propionate-(E)-trimethylsilyl-enol ether, methyl propionate-(Z)-trimethylsilyl-enol ether, isopropyl propionate-(E)-trimethylsilyl-enol ether, isopropyl propionate-(Z)-trimethylsilyl-enol ether, phenyl propionate-(E)-trimethylsilyl-enol ether, phenyl propionate-(Z)-trimethylsilyl-enol ether, phenyl isobutyrate-trimethylsilyl-enol ether, 3-pentanone-(E)-trimethylsilyl-enol ether, 3-pentanone-(Z)-trimethylsilyl-enol ether, 2-pentanonetrimethylsilyl-enol ether, propiophenone-(E)-trimethylsilyl-enol ether, propiophenone-(Z)-trimethylsilyl-enol ether, t-butyl thiopropionate-(E)-trimethylsilyl-enol ether, t-butyl thiopropionate-(Z)-trimethylsilyl-enol ether, ethyl thiopropionate-(E)-trimethylsilyl-enol ether, ethyl thiopropionate-(Z)-trimethylsilyl-enol ether, and S-ethyl thioacetate-trimethylsilyl-enol ether.

These silyl-enol ethers are easily synthesized from the corresponding ketones, esters or thioesters in accordance with the processes described in E.W. Colvin, Silicon in Organic Synthesis, pp. 198-287, Butterworths, London (1981) and N. Slougui, et al., Synthesis, p. 58 (Jan., 1982).

The following process may be mentioned as an instance of general synthesis of the silyl-enol ether. A dialkylamine is dissolved in tetrahydrofuran. The solution is cooled to about 0°C, and a solution of n-butyl lithium in tetrahydrofuran, etc. is added thereto dropwise to prepare a lithium dialkylamide solution. The solution is cooled to about -78°C, and a ketone, an ester or a thioester is added to the solution dropwise. After about 30 minutes, a silyl chloride derivative is added thereto, followed by allowing the mixture to sufficiently react at that temperature. After the reaction, the salt formed is removed by filtration. The separated salt and the reaction container are washed with pentane, and the washing is combined with the filtrate. The combined solution is distilled to remove pentane, and the residue is further distilled to obtain a desired silyl-enol ether.

Specific examples of the substituted aldehyde represented by formula (III) include acetaldehyde, ethanal, propanal, butanal, methoxymethylaldehyde, ethoxymethylaldehyde, propyloxymethylaldehyde, butyloxymethylaldehyde, benzyloxymethylaldehyde, methyl glyoxylate, ethyl glyoxylate, isopropyl glyoxylate, n-butyl glyoxylate, and t-butyl glyoxylate. The glyoxylic esters can be prepared by, for example, the process of T. Ross Kelly, et al. (see Synthesis, pp. 544-545 (1972)).

The optically active binaphthol-titanium complex represented by formula (IV) which can be used as a catalyst in the present invention can be prepared by, for example, the process disclosed in JP-A-2-40344 (the term "JP-A" as used herein means an "unexamined published Japanese patent application"). In more detail, a titanium tetrahalide (halogen: chlorine or bromine) and titanium tetraisopropoxide are mixed in hexane to prepare titanium dihalogenodiisopropoxide crystals, which are then dissolved in toluene. Separately, at least 0.5 g, per mmol of the substrate, of Molecular Sieve 4A powder (a commercially available product) is added to methylene chloride. The above-prepared titanium dihalogenodiisopropoxide toluene solution and then binaphthol were successively added thereto, followed by stirring for about 1 hour to obtain a binaphtholtitanium complex (IV).

The binaphthol-titanium complex (IV) takes an (R)-form when synthesized from (R)-binaphthol or an (S)-form when synthesized from (S)-binaphthol. A choice of the isomeric form is made according to the absolute configuration of a desired optically active β-hydroxyketone (I). That is, the use of (R)-binaphthol provides an optically active β-hydroxyketone (I) having (R) configuration with respect to the hydroxyl group.

In carrying out the present invention, it is preferred that a silyl-enol ether (II) and an almost equimolar amount of a substituted aldehyde (III) are added to a solution of a binaphthol-titanium complex (IV) in an organic solvent and allowed to react. It is preferred that the respective concentrations of the silyl-enol ether (II) and the substituted aldehyde (III) in the organic solvent are approximately from 0.1 to 5 mol/ℓ.

Usable organic solvents include halogenated hydrocarbons, e.g., methylene chloride, chloroform, and carbon tetrachloride; aromatic hydrocarbons, e.g., benzene and toluene; aprotic solvents, e.g., tetrahydrofuran, diethyl ether, and dimethoxyethane. Among them, methylene chloride and toluene are preferred.

For obtaining a product in high optical yield, the binaphthol-titanium complex (IV) is preferably used in an amount of approximately from 0.02 to 1 mol, and more preferably approximately from 0.05 to 0.1 mol, per mol of the resp ctive amounts of the silyl-enol ether (II) and th substitut d aldehyde (III), i.e., p r mol of th amount of th silyl-enol ether (II) and per m l of th amount of the substituted ald hyde (III).

Th pr ferred reaction temp rature is approximately from -50° t 0°C, and particularly pref rred reaction temp ratur is appr ximately from -30° t -10°C. Th pr ferred reaction tim is approximately from 3 t 20 h urs.

After compl tion of th r action, an alkali, .g., a sodium hydrog ncarbonat aqueous solution, is added

to the reaction mixture, and the mixture is xtracted with a solvent, e.g., diethyl ther or ethyl acetate. After drying, the solvent f th xtract is vaporated, and th residu is purified by column chromatography on silica g l, etc. to obtain a desired optically active β-hydroxyketone (I) in high yield.

The present invention will now be illustrated in greater detail with reference to Examples, but the present invention should not be construed as being limited thereto. All the percents are by weight unless otherwise indicated.

Analyses in Examples were conducted by means of the following instruments or under the following conditions.

^{1}H-NMR:	GEMINI 300 (300 MHz), manufactured by VARIAN Co,. Ltd.
^{13}C-NMR:	GEMINI 300 (75 MHz), manufactured by VARIAN Co., Ltd.
Optical Rotation:	Polarimeter DIP-370, manufactured by JEOL Ltd.

The syn-anti ratio was decided from the integrated value of NMR in accordance with the method of J. Canceill, et al., Bull. Soc. Chim. Fr., pp. 1024-1030 (1967) and Topics in Stereochemistry, Vol. 13, p. 1, John Wiley & Sons, Inc. (1982).

The enantiomer excess (% ee) was determined by ^{1}H-NMR analysis on the α-methoxy-α-trifluoromethylphenylacetic acid ester of the product obtained in accordance with the process of D. Parker, et al., Chem. Rev., Vol. 91, pp. 1441-1457 (1991) or the process of J.A. Dale, et al., J. Org. Chem., Vol. 34, pp. 2543-2549 (1969).

EXAMPLE 1

In a 50 mℓ Schlenk flask purged with argon were charged 2.98 mℓ (10 mmol) of titanium tetraisopropoxide and 5 mℓ of hexane, and 1.10 mℓ (10 mmol) of titanium tetrachloride was added thereto. The mixture was stirred at room temperature for 10 minutes, followed by allowing to stand at room temperature for 3 hours whereupon white crystals precipitated. The solvent was withdrawn by means of a syringe, and the crystals were recrystallized from 5 mℓ of hexane. Removal of the solvent and subsequent recrystallization were repeated twice. Drying under reduced pressure gave 3.09 g of white titanium dichlorodiisopropoxide. The product was dissolved in 43 mℓ of toluene to prepare a 0.3 mol/ℓ solution.

Separately, 0.5 g of Molecular Sieve 4A powder (a product of Aldrich Co.) was put in a 25 mℓ flask. After purging with argon, 3 mℓ of toluene was added to the flask. Thereafter, 6.7 mℓ (2 mmol) of the above-prepared toluene solution of titanium dichlorodiisopropoxide and 573 mg (2 mmol) of (R)-binaphthol were added thereto, followed by stirring at room temperature for 1 hour to obtain an (R)-binaphthol-titanium complex (hereinafter designated (R)-1).

0.5 ml (0.1 mmol) of the resulting solution was cooled to 0°C in an ice bath, and 157 mg (1 mmol) of (Z)-3-trimethylsilyloxy-2-pentene (86% Z) was added thereto. To the mixture were added 130 mg (1 mmol) of freshly distilled n-butyl glyoxylate and 0.5 mℓ of methylene chloride, and the system was allowed to react at 0°C for 0.5 hour.

The reaction mixture was poured into 10% hydrochloric acid-methanol cooled to 0°C. The solution was filtered through Celite, and the filtrate was extracted three times with a 5 mℓ portion of diethyl ether. The organic layer combined was washed with a saturated sodium chloride aqueous solution and dried over magnesium sulfate. The solvent was removed by distillation, and the residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate=15/1 by volume) to obtain 135 mg (yield 63%) of n-butyl 2-hydroxy-3-methyl-4-oxohexanonate.

$[\alpha]_D^{26}$: +5.0° (c=1.0, CHCℓ$_3$) (98% syn; 99% ee)

IR (neat): 3500, 2970, 1730, 1460, 1260, 760 cm^{-1}

Syn-isomer:

^{1}H-NMR (CDCℓ$_3$) δ:	0.94 (t, J=7.4Hz, 3H), 1.07 (t, J=7.0Hz, 3H), 1.15 (d, J=7.3Hz, 3H), 1.38 (m, 2H), 1.65 (m, 2H), 2.56 (q, J=7.0Hz, 2H), 2.94 (dq, J=3.9, 7.4Hz, 1H), 3.12 (d, J=4.6Hz, 1H), 4.20 (d, J=6.7Hz, 2H), 4.56 (dd, J=3.9, 4.6Hz, 1H)
^{13}C-NMR (CDCℓ$_3$) δ:	7.6, 10.8, 13.7, 19.1, 30.6, 34.2, 49.2, 65.9, 71.2, 173.5, 211.8

Anti-isomer :

^{1}H-NMR (CDCℓ3) δ:	3.04 (m, 1H), 3.30 (d, J=7.6Hz)
^{13}C-NMR (CDCℓ$_3$) δ:	7.5, 13.1, 15.3, 19.0, 30.5, 34.8, 49.1, 65.6, 72.8, 173.5, 211.7

EXAMPLE 2

(1) Butyl 2-Hydr xy-4-(trimethylsilyl)oxy-4-heptanoate (int rmediate):

0.5 ml (0.1 mmol) of (R)-1 solution prepared in the same manner as in Example 1 were cooled to 0°C, and 157 mg (1 mmol) of 2-trimethylsilyloxy-1-pentene and subsequently 130 mg (1 mmol) of freshly distilled n-butyl glyoxylate and 0.5 mℓ of methylene chloride were added thereto, followed by allowing the mixture to react at 0°C for 0.5 hour. The solution was poured into 10% hydrochloric acid-methanol cooled to 0°C. The solution was filtered through Celite, and the filtrate was extracted three times with a 5 mℓ portion of diethyl ether. The organic layer combined was washed with a saturated sodium chloride aqueous solution and dried over magnesium sulfate. The solvent was removed by distillation, and the residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate=15/1 by volume) to obtain 143 mg (yield 67%) of n-butyl 2-hydroxy-4-oxoheptanoate.

$[\alpha]_D^{25}$: +5.9° (c=1.0, $CHC\ell_3$) (99% ee)

IR (neat): 3470, 2970, 1720, 1460, 1260, 760 cm^{-1}

^1H-NMR ($CDC\ell_3$) δ:	0.91 (t, J=7.4Hz, 3H), 0.92 (t, J=7.3Hz, 3H), 1.37 (m, 3H), 1.61 (m, 2H), 1.62 (m, 2H), 2.42 (q, J=7.3Hz, 2H), 2.67 (br, 1H), 2.85 (dd, J=6.0, 17.3Hz, 1H), 2.93 (dd, J=4.5, 17.3Hz, 1H), 4.18 (t, J=6.7Hz, 2H), 4.45 (dd, J=4.5, 6.0Hz, 1H)
^{13}C-NMR ($CDC\ell_3$) δ:	13.7, 17.0, 19.1, 30.6, 45.4, 46.0, 65.8, 67.1, 173.9, 208.5

EXAMPLE 3

0.5 ml (0.1 mmol) of (R)-1 solution prepared in the same manner as in Example 1 were cooled to 0°C, and 190 mg (1 mmol) of (E)-1-ethylthio-l-trimethylsilyloxy-l-propene (77% E) and subsequently 130 mg (1 mmol) of freshly distilled butyl glyoxylate and 0.5 mℓ of toluene were added thereto, followed by allowing the mixture to react at 0°C for 0.5 hour. The resulting mixture was poured into 10% hydrochloric acid-methanol cooled at 0°C. The solution was filtered through a pad of Celite, and the filtrate was extracted three times with a 5 mℓ portion of diethyl ether. The combined organic layer was washed with a saturated sodium chloride aqueous solution, dried over magnesium sulfate and evaporated under reduced pressure to remove the solvent. The residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate=15/1 by volume) to obtain 158 mg (yield 64%) of n-butyl 4-ethylthio-2-hydroxy-3-methyl-4-oxobutyrate.

$[\alpha]_D^{26}$: +5.0° (c=1.0, $CHC\ell_3$) (98% syn; >99% ee)

IR (neat): 3500, 2970, 1730, 1460, 1260, 760 cm^{-1}

Syn-isomer:

^1H-NMR ($CDC\ell_3$) δ:	0.94 (t, J=7.4Hz, 3H), 1.23 (d, J=7.2Hz, 3H), 1.27 (t, J=7.5Hz, 3H), 1.39 (m, 2H), 1.66 (m, 2H), 2.91 (q, J=7.5Hz, 2H), 3.06 (dq, J=3.6, 7.2Hz, 1H), 3.19 (br, 1H), 4.22 (t, J=6.7Hz, 2H), 4.59 (d, J=3.6Hz, 1H)
^{13}C-NMR ($CDC\ell_3$) δ:	11.5, 13.7, 14.6, 19.1, 23.5, 30.6, 51.3, 71.6, 173.2, 200.9

Anti-isomer:

^1H-NMR ($CDC\ell_3$) δ:	0.94 (t, J=7.4Hz, 3H), 1.35 (d, J=7.3Hz, 3H), 1.38 (m, 2H), 1.67 (m, 2H), 2.08 (d, J=7.5Hz, 2H), 3.12 (m, 1H), 3.35 (br, 1H), 4.18 (m, 2H), 4.25 (m, 1H)
^{13}C-NMR ($CDC\ell_3$) δ:	14.1, 23.4, 51.2, 65.8, 72.8, 173.1, 200.7

EXAMPLE 4

An (S)-binaphthol-dichlorotitanium complex solution was prepared in the same manner as the preparation of the (R)-binaphthol-dichlorotitanium complex solution in Example 1 except that (S)-binaphthol was used in place of (R)-binaphthol. 0.5 ml (0.1 mmol) of the (S)-binaphtholdichlorotitanium complex solution were cooled to 0°C, and 218 mg (1 mmol) of (E)-1-t-butylthio-1-trimethylsilyloxy-1-propen (93% E) and subsequently 88 mg (1 mmol) of freshly distilled methyl glyoxylate and 0.5 mℓ f toluene were added th reto, followed by allowing the mixture to react at 0°C for 2 hours. The resulting mixture was poured into 10% hydrochloric acid-methanol cooled at 0°C. The solution was filtered through a pad of Celite, and the filtrate was extracted three times with a 5 mℓ portion of diethyl ether. The combined organic layer was washed with a saturated sodium

chloride aqueous solution, dried ov r magnesium sulfate, and evaporated under reduced pressure to remove th solvent. The residue was purified by silica gel column chromatography (eluent: hexane/ethyl acetate=15/1 by volume) to obtain 186 mg of methyl 4-t-butylthio-2-hydroxy-3-methyl-4- x butyrat in a yield of 80% (16% syn, 84% ee; 84% anti, 93% ee).

IR (neat): 3500, 2970, 1720, 1460, 1260, 1190, 760 cm^{-1}

Syn-isomer:

^{1}H-NMR ($CDCl_3$) δ:	1.30 (d, J=7.2Hz, 3H), 1.45 (s, 9H), 3.02 (dq, J=4.4, 7.2Hz, 1H), 3.12 (br, 1H), 3.79 (s, 3H), 4.23 (d, J=4.4Hz, 1H)
^{13}C-NMR ($CDCl_3$) δ:	14.1, 29.8, 48.5, 51.5, 52.6, 73.1, 173.5, 201.9

Anti-isomer:

^{1}H-NMR ($CDCl_3$) δ:	1.20 (d, J=7.1Hz, 3H), 1.47 (s, 9H), 2.97 (m, 1H), 3.80 (s, 3H), 4.54 (d, J=4.1Hz, 1H)
^{13}C-NMR ($CDCl_3$) δ:	11.9, 51.7, 52.8, 71.8

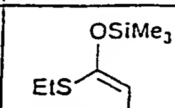
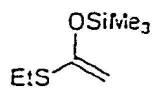
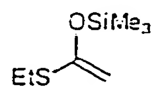
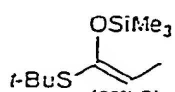
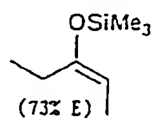
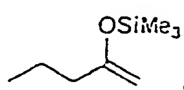
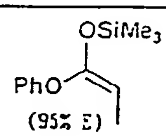
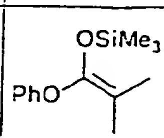
EXAMPLES 5 TO 12

The following Examples were carried out in the same manner as in Example 1, except for changing the reaction substrates and the solvent as shown in Table below. The obtained products and the reaction results are shown In Table.

The following abbreviations are used in Table.

Me: a methyl group
Et: an ethyl group
Bu: a butyl group
Ph: a phenyl group
Bn: a benzyl group

Table

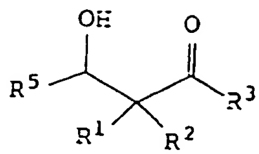
Example	Silyl-enol Ether	R^5CHO	Solvent	Y*	syn(%ee)	anti(%ee)
5	 (91% Z)	BuO_2CCHO	toluene	87	68(98%ee)	32(51%ee)
6		$BnOCH_2CHO$	toluene	81	(94%ee)	
7		$BnOCH_2CHO$	CH_2Cl_2	71	(91%ee)	
8	 (93% E)	BuO_2CCHO	toluene	81	20(69%ee)	80(86%ee)
9	 (73% E)	BuO_2CCHO	CH_2Cl_2	64	98(99%ee)	2(-)
10		$BnOCH_2CHO$	CH_2Cl_2	50	(89%ee)	
11	 (95% E)	BuO_2CCHO	toluene	80	54(90%ee)	46(80%ee)
12		BuO_2CCHO	toluene	71	(80%ee)	

*) Yield (%)

It can be seen from the above results that an optically active β-hydroxyketone can be obtained efficiently with high diastereo-selectivity and high enantio-selectivity by using the optically active binaphthol-titanium complex.

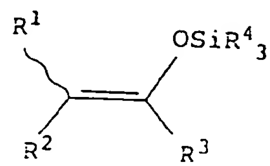
Claims

1. A process for producing an optically active β- hydr xyket n repres nted by formula (I):



(I)

wherein R^1 and R^2, which may be the same or different, each represent a hydrogen atom or a lower alkyl group; R^3 represents a lower alkyl group, a lower alkyloxy group, a phenyl group, a phenyloxy group or a lower alkylthio group; and R^5 represents a lower alkyl group, a lower alkyloxymethyl group, a benzyloxymethyl group or a lower alkyloxycarbonyl group,
comprising reacting a silyl-enol ether represented by formula (II):



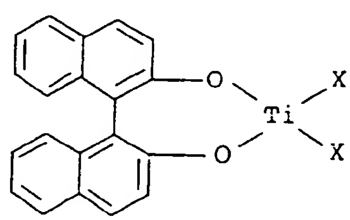
(II)

wherein R^1, R^2, and R^3 are as defined above; and three R^4s, which may be the same or different, each represent a lower alkyl group or a phenyl group, with a substituted aldehyde represented by formula (III):

R^5CHO (III)

wherein R^5 is as defined above,

in the presence of a binaphthol-titanium complex represented by formula (IV):



(IV)

wherein X represents a chlorine atom or a bromine atom.

2. A process as claimed in claim 1, wherein the reacting is conducted in an organic solvent.

3. A process as claimed in claim 1 or 2, wherein the respective concentrations of the silyl-enol ether and the substituted aldehyde in the organic solvent are approximately from 0.1 to 5 mol/ℓ.

4. A process as claimed in claim 1, 2 or 3, wherein the binaphthol-titanium complex is present such that the amount of the binaphthol-titanium complex is approximately from 0.02 to 1 mol per mol of the respective amounts of the silyl-enol ether and the substituted aldehyde.

5. A process as claimed in claim 1, 2, 3 or 4, wherein the reacting is conducted at a temperature of approximately from -50°C to 0°C.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 94 30 1766

Category	DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
P,X	CHEMICAL ABSTRACTS, vol. 119, no. 19, 8 November 1993, Columbus, Ohio, US; abstract no. 202959, MIKAMI K ET AL 'Enantioselective and diastereoselective catalysis of the Mukaiyama aldol reaction: ene mechanism in titanium-catalyzed aldol reactions of silyl enol ethers' * abstract * & J. AM. CHEM. SOC. (JACSAT,00027863);93; VOL.115 (15); PP.7039-40 TOKYO INST. TECHNOL.;DEP. CHEM. TECHNOL.; TOKYO; 152; JAPAN (JP)	1-5	C07C45/51
X	CHEMISTRY AND INDUSTRY vol. 23 , 1986 , LONDON page 824 M.T. REETZ ET AL. 'Enantioselective C-C bond formation with chiral Lewis acids.' * the whole document *	1-5	
Y	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY. vol. 111 , 1989 , GASTON, PA US pages 1940 - 1941 K. MIKAMI ET AL. 'Asymmetric Glyoxylate--Ene Reaction Catalyzed by Chiral Titanium Complexes: A Practical Access to alpha - Hydroxy Esters in High Enantiomeric Purities.' * the whole document *	1	TECHNICAL FIELDS SEARCHED (Int.Cl.5) C07C
Y	SYNTHESIS. 1977 , STUTTGART DE pages 91 - 110 J.K. RASMUSSEN 'O-Silylated Enolates - Versatile Intermediates for Organic Synthesis.' * page 107 - page 108 *	1	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	4 May 1994	Bonnevalle, E

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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E : earlier patent document, but published on, or after the filing date
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L : document cited for other reasons

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